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JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY

Effect of Cortisone in Treatment of Psychotic Illnesses

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The rapidly growing interest in the use of cortisone and ACTH in the treatment of psychotic illnesses, particularly schizophrenia, had its beginnings in the observable side effects produced by these drugs in arthritic patients. Such reactions as euphoria, mania, and depression suggested that the drugs were of great potential value for psychiatry. Successful clinical trials continue to emphasize the need for a more thorough understanding of the relationship between endocrine balance and mental illness. Meanwhile, this hopeful application of adrenal steroids as a new and promising form of psychiatric therapy has posed a great many questions requiring investigation. The beneficial effects of cortisone administered to several chronic schizophrenic patients prompted a controlled study designed to test the various theories which might explain these results.

BACKGROUND

Pincus and Hoagland at the Worcester Institute were among the first to demonstrate an altered adrenocortical status in schizophrenia. Their early papers[12, 21] showed that schizophrenic patients had a decreased adrenocortical response to both internal and external types of stress. In their latest study,[13] they conclude that "schizophrenic patients showed lower than normal rates of excretion of corticoids and phosphates and thus displayed at rest evi-

This study was supported by a grant from the Ohio Department of Public Welfare, Division of Mental Hygiene, under the guidance of Doctor Lowell O. Dillon, Commissioner.

dence of both hyperadrenalism and of hypoadrenalism." A decrease in the excretion of urinary cortins is interpreted as evidence of hypoadrenalism and an increase in 17-ketosteroid excretion as hyperadrenalism. At the same time, they raise the possibility of qualitative alterations in adrenocortical output, an approach which may well prove more enlightening than one dealing with simple quantitative changes in adrenocortical function.

Sackler et al[29, 30, 37] have taken a position different from that of the Worcester group. They believe that the decreased adrenocortical activity, reported by the latter workers, may be attributed to a depleted adrenocortical reserve in association with an absolute, relative, or operative hyperadrenocorticism rather than to a nonresponsive gland. Their emphasis is on the operative effect of the adrenals in relation to total adrenocortical output, counteracting hormonal antagonists, and end organ sensitivity.

Investigators have tried many different indices of adrenocortical function, and as yet no one index has proved satisfactory to everyone. Circulating eosinophils were at first used by Pincus and Hoagland,[12, 21] Altschule,[3] Parsons et al,[20] and in our preliminary studies.[8, 9] Seventeen-ketosteroid excretion in urine, uric acid excretion, potassium and sodium levels, and creatine-uric acid ratios have all been selected as measures of adrenocortical function. Hemphill and Reiss et al[25] attempted to combine several of these indices; Pincus and Hoagland have computed a total response index based on some of them. However, their interesting results failed to clarify the problem of finding a single reliable index. The use of urinary cortins as an index in the most recent Worcester study[13] is an important trend toward more direct measurement of adrenocortical function rather than its reflection by end organs. They found significant differences in cortin excretion between schizophrenic and normal groups, but Altschule[1] reports that the rises in urinary corticoids after the ingestion of carbohydrate or an ACTH injection are the same in both schizophrenic and normal subjects.

Various stimuli, such as the pursuit meter, target ball, mirror drawing, pain, glucose, corticotropin,[13, 19] create controlled conditions of stress to test the reactions of the adrenals in schizophrenics. Using the Rosensweig frustration test as a stimulus and measuring blood pressure, pulse, respiration, and galvanic skin inductance as indices, Jurko et al[14] presented evidence that schizophrenics reacted differently than did normal and psychoneurotic groups. Altschule[1] has criticized the conclusion that the adrenal cortex in schizophrenia does not respond normally to stress without determining first whether the test conditions actually constitute a stress to psychotics.

More recently, Gerard and Phillips[11] published a paper correlating subjects' socioeconomic attainment and their adrenocortical response to stress. They found that persons of higher social attainment were less stressed on the basis of 17-ketosteroid scores than subjects of lower status. One might infer from this that education and living in so-called higher cultures tend to permit the organism to adapt more economically to stress. Richter's study[26, 27] of the domestication of the Norway rat, if paralleled in man's evolution, leads to the theoretic assumption that modern man is deficient in adrenal secretion and is less able physiologically to cope with stress.

Several articles have been written describing the effects of adrenocortical hormones on the nervous system. Torda and Wolff[36] studied the electroencephalographic changes induced

in rats by prolonged administration of ACTH and observed a decrease of electrical activity due mainly to a shift in electrolytes. The anatomic study by Castor and his associates[7] revealed degeneration of the paraventricular areas of the hypothalamus in cortisone-treated animals. This study seemed so important that we have repeated it and will publish our results in a separate paper.

Cerebral blood flow studies in schizophrenics have been previously reported. Kety et al[15] found cerebral blood flow and cerebral oxygen consumption to be identical in schizophrenic and normal subjects. Altschule[2] has suggested that factors modifying cerebral blood flow may be responsible for the occurrence of hallucinations in schizophrenia. Sensenbach et al[33] recently found significant increases in mean cerebral vascular resistance and mean arterial blood pressure in 9 subjects receiving 100 to 200 mg. cortisone daily. Accordingly, it was felt that careful cerebral blood flow and metabolism studies of our patients before and after treatment with cortisone might yield valuable information as to the target effects of high doses on the brain. These studies will also be prepared separately.

The literature on the treatment of psychotic patients with cortisone is small. Aside from the two mentioned above,[8, 9] Rees's[24] paper appears to be the only other published report. While he found no significant changes after four days of treatment, this short period, in our opinion, could not be expected to produce any important reactions. In a personal communication, Polatin[22] stated that he has had poor results in attempting to duplicate the treatment described in our earlier papers.

The diversity of results in controlled experiments are usually due to different methodologies. In this experiment and in the previous clinical trials, large doses of cortisone, ranging from 300 to 800 mg. daily were administered without fear of precipitating a psychotic break, the subjects being psychotics. Other workers[10] have indicated that prolonged high dosage with cortisone leads to reversible adrenal atrophy. Prolonged treatment with cortisone may produce at least partial adrenal atrophy associated with improvement in the patients' mental status. The point at issue is not entirely whether the adrenal gland is hyperfunctioning or hypofunctioning. Qualitative rather than quantitative changes in adrenocortical output may be the key to understanding the relationship between the endocrine system and mental illness.

Benda's paper[6] on the application of the general adaptation syndrome to psychiatry is the most complete analysis yet published. The monumental work of Selye[32] has stimulated many such attempts to apply his concepts of stress and triphasic response to the understanding of the psychoses. His work gives us a new framework to view the many contributions to this field.

METHOD

Two groups were utilized in this study, an experimental and a control group. The experimental group was treated with cortisone,* while the control group received only placebos.†

* The cortisone was generously supplied by the Medical Division, Merck & Company, Rahway, New Jersey.

† Placebos were supplied by Strong, Cobb, & Company.

In every other possible way both groups were treated alike in terms of ward care and testing procedures. All patients received medication or the placebo for a period of four weeks. The patient's body weight and skeletal structure were the determining factors in estimating the original dosage levels. The average daily dose for the experimental patients was approximately 400 mg. with a range of 300 to 500 mg. The dose was divided in two equal portions, one-half being administered after breakfast and the other half after luncheon. Dosage was more or less constant except in 3 cases where treatment was halted for about three days because of episodes of renal colic, which may have been related to the administration of the cortisone.

TESTS AND EVALUATIONS BEFORE, DURING, AND AFTER TREATMENT

A psychologic battery of tests was administered before the start and again during the last week of treatment. Tests included in the battery were the Rorschach, Wechsler-Bellevue Intelligence Scale for Adults, Bender-Gestalt, figure drawings, and the Runner-Seaver personality test. Form I of the Wechsler-Bellevue was used in the pretreatment testing and Form II in the final psychologic examination.

A psychiatric rating scale was filled out twice a week for six weeks, beginning one week prior to treatment and ending one week after termination of the treatment. The rating scale with a scoring range of 22 to 154 was a slight modification of the one devised by Malamud and Sands.[31] Of the 24 items, 4 were filled out by ward nurses (sleep, eating, work, and sexual behavior). The other 18 items, which dealt with such variables as appearance, awareness, subjective reorganization, affect, etc., were rated independently by the psychologist and psychiatrist for the first sixty observations. Since interrater reliability was high (product-moment $r = +.86$), the remaining ratings were performed by the psychologist alone.

Three tests of adrenocortical function were employed. Seventeen-ketosteroid excretion was determined in the week preceding therapy and in the final week of treatment. Circulating eosinophils were estimated three times a week throughout the study at approximately the same hour in order to rule out the normal fluctuation during the 24 hour period. ACTH responsivity (Thorn test) was measured on two occasions, the week preceding treatment and the last week. Twenty-five mg. ACTH were injected intramuscularly, and percentage changes in the eosinophil level were calculated.

In addition, pretherapy and post-therapy electroencephalograms were taken, using an eight-channel Grass machine with an electronic recording analysis as determined on an Offner Analyzer. A similar time procedure was followed for chest x-rays, which were read by a radiologist independent of the project. Cerebral blood flow and metabolism studies were made in the same fashion. Each patient received a complete physical examination before and after treatment by an internist well-versed in endocrinologic changes and unaware of whether the subject was receiving placebo or cortisone. Finally, a detailed social history was obtained prior to treatment, and the patient was classified as having "good" or "poor" prepsychotic adjustment.

The above methodology was designed in so far as possible to answer the following series of questions:

(1) Does the use of cortisone help in the psychoses?
(2) In what type of psychotic disturbance is it useful?
(3) At what stage of a psychotic illness is it of value, and after what previous treatment does it seem indicated?
(4) In what dosage does it prove beneficial, and over what period is it necessary to administer this specified dose?
(5) Which indices best indicate what patients can respond to this type of treatment?
(6) Why do patients who respond to this type of treatment show this improvement, and why do patients who fail to improve show no change in their condition?

(7) Will any toxic psychotic symptoms occur, or will any other difficulties arise in the treatment of these patients which can be attributed to the use of cortisone?
(8) What effect does cortisone have on the nervous system as manifested by changes in cerebral blood flow and metabolism, pathologic structure of the brain, and electroencephalographic records?

CHARACTERISTICS OF THE SAMPLE

The experiment had to be terminated near the halfway mark with only 27 of the 50 planned studies completed. For this reason, the number of patients in the control group is too small and cannot be compared to the experimental group. Table I lists the relevant diagnostic information regarding the sample.

TABLE I

Patients in Experimental and Control Groups

Diagnosis	Total No.	No. E	Per cent of Total	No. C	Per cent of Total
Paranoid Schizophrenia	7	6	22.2	1	3.7
Catatonic Schizophrenia	9	7	25.9	2	7.4
Hebephrenic Schizophrenia	3	3	11.1	0	—
Simple Schizophrenia	2	2	7.4	0	—
Chronic Schizophrenia (Undifferentiated)	2	1	3.7	1	3.7
Manic-Depressive, Manic	2	1	3.7	1	3.7
Involutional Depression	2	1	3.7	1	3.7
Total	27	21	77.7	6	22.2

All patients came from the research ward of the Cleveland Receiving Hospital. They were disturbed, regressed males, so-called treatment failures, who had not responded previously to electrocoma therapy, insulin, or lobotomy. Most of the subjects had undergone several courses of treatment, and many of them had had electrocoma therapy within a week prior to being placed on the cortisone program. All the patients could be regarded as chronically ill; the probability of their improving with the usual treatment methods was considerably less than that of patients in the acute stages of psychiatric disorders. Each subject was assigned to either the experimental or control group by the psychiatrist in charge, and the designation was known only by the nurse who administered the medication. Since the psychiatrist did not rate the subjects after the original test period, bias from that source was eliminated.

RESULTS

Clinical Results: Of the 21 experimental patients, 9 (42.8 per cent) showed a significant improvement within one month after termination of the cortisone treatment. Six of the 9

patients were discharged shortly thereafter as "improved." Four patients in the responding group received electrocoma therapy after the cortisone period ended. It was noted that their response to the shock treatments was better than in the past, although the reason for this is unknown. The remaining 3 improved patients are still hospitalized. While better adjusted than before cortisone therapy, they have not improved sufficiently to be discharged.

Psychological Results: Four patients in the experimental group could not be tested in the post-treatment period because of mutism or stupor. The post-treatment Rorschach of 1 manic patient could not be tabulated or statistically evaluated due to exacerbation of his symptoms.

With respect to the Wechsler-Bellevue I. Q. and the behavior rating scores, the experimental group as a whole shows no statistically significant over-all improvement compared to its pre-experimental status (table II).

No apparent major changes were revealed in the figure drawing test, which throws light on the individual's concept of self, or in the Bender-Gestalt test for psychomotor functioning. Very few patients exhibited radical changes for the better on the Rorschach. Where noticeable improvement did occur, the adjustment attained was extremely brittle, consisting largely of personal constriction and superficiality but with a diminution of autistic tendencies and confusion. The changes were of quantity and not quality. Most of the

TABLE II

Pretreatment and Post-treatment I. Q. and Behavior Rating Scores for the Experimental Group

Measure	Mean Pre-Rx	Mean Post-Rx	Difference	t
Wechsler-Bellevue	78.4	81.3	2.9	0.89*
Behavior Rating	67.6	66.8	—0.8	0.22*

* Not statistically significant.

TABLE III

Pretreatment and Post-treatment Rorschach Variables in the Experimental Group

Variable	Mean Pre-Rx	Mean Post-Rx	Difference	t
F+ %	54.81	72.00	17.19	2.91*
Number of responses	11.67	14.00	2.33	0.29†
Initial reaction time (seconds)	32.82	29.52	3.30	0.88†
Number of M+ responses	0.5	0.875	0.375	2.64*
Number of cards failed or rejected	2.37	1.06	1.31	4.14*
Number of O− responses	3.20	2.47	0.73	0.70†
Number of popular responses	3.25	3.94	0.69	0.79†
Number of FC+ responses	0.75	0.375	0.375	0.85†

* Significant at or beyond the .01 level of confidence.

† Not statistically significant.

subjects were still psychotic in character in the post-treatment period, although they tended to be "less" psychotic.

The Rorschach protocols of the experimental patients who finished both pretreatment and post-treatment psychologic batteries were analyzed (table III).

The atomistic type of analysis admittedly does not give an integrated picture of change, but it is a rough index of progress. Initial reaction time to the Rorschach cards indicates speed of reactivity, and excessive delay is frequently a sign of retardation, blocking, overcautiousness, or evasiveness. Mean reaction time was slow in our patients who showed no significant improvement after cortisone treatment. The number of responses is a sign of intellectual productivity and range of interests, a measure low in the group both before and after therapy. F+, the percentage of accurately perceived responses in a record, throws light on the extent and adequacy of reality testing. The experimental group average was well below the normal level in the pretreatment phase but improved considerably in the second testing. The number of M+ in a record is a gauge of ability to think creatively, to tolerate frustration, to be imaginative. Although still abnormally low, the patients exhibited significant improvement in this area. No improvement was noted in three indices: (1) FC+, an index of emotional control and affective rapport with the individual's environment; (2) popular responses, one test of the ability to think conventionally; and (3) O– responses, an index of distorted, peculiar thinking. There was significant change in the number of cards failed or rejected. Here a decrease means the subjects were less blocked, apathetic, negativistic, or cautious. In any event, they exerted more effort to deal with the situation instead of escaping from it.

Performance on cards VIII–X, the bright colored cards, was also classified. How an individual handles these cards is generally taken to indicate the way he characteristically deals with emotional stress in everyday life. All subjects revealed impairment in this area on the first test record, but 44 per cent improved on the second record, if only to a small degree. Of the patients who improved clinically, one-half showed emotional improvement on cards VIII–X. The ratio was similar for patients who did not make any clinical progress.

Every patient able to cooperate filled out the Runner-Seaver questionnaire[28] before and after his course of therapy.* This questionnaire is a paper and pencil personality inventory consisting of 239 statements, which the testee marks as true, false, uncertain if true, or uncertain if false. The scoring relates the individual's standing with respect to a normal standardization group on 27 personality factors ranging from zest and routine orderliness to emotional ambivalence and overdependence. The distribution of scores for the test group is compared with the standard by means of the Chi-square test of significance.

The results reported here include only the responses of the schizophrenic patients in the experimental group. Before treatment with cortisone, they differed significantly from the norm with respect to five factors. The three factors accepted most frequently were: (1) identification with and warmth of response to others, (2) readiness to feel guilty about ex-

* This study was performed by Mrs. Margaret A. Seaver.

pressing warmth or affect toward others, and (3) parsimony or psychologic "withholding." On the other hand, the two factors rejected most often were: (1) self-reliance and (2) initiative. Before cortisone treatment, then, the schizophrenic patients as a whole revealed an inability to handle stimulation and inhibition in responding to feelings of warmth. They did not exhibit overt activity to stimuli and instead were overcome by all or no emotional reactions which they tried to cope with by withholding all outwardly directed cathexis.

The same group diverged from normal on eight factors following cortisone treatment. There was no longer a greater acceptance of emotional parsimony along with an identification with and warmth of response to others. Three of the pretreatment findings still present were: (1) a readiness to feel guilt in the expression of affect, (2) a lack of self-reliance, and (3) a lack of initiative. New trends also emerged after therapy: (1) rejection of the need for immediacy of response, (2) acceptance of a withdrawal factor, (3) acceptance of the negativism factor, and (4) focusing of attention on external objects indicated by acceptance of the "things" and "routine orderliness" factors.

The group's psychologic status after treatment still reveals inhibition and a lack of self-reliance and initiative. However, overt attempts were being made to solve personal conflicts. Impulsiveness had decreased, and, despite continuing withdrawal and negativism, the group was no longer overwhelmed by affective stimuli. Even though it is not a healthy or a desired adjustment, it does seem more adaptive than before treatment.

Physiologic Results: Both the ACTH responsivity test and 17-ketosteroid counts were significantly different in the post-therapy period. The 17-ketosteroid counts were higher and the percentage drop in circulating eosinophils lower than at the onset of the treatment.

Separate analyses of ACTH responsivity and 17-ketosteroid excretion data were made for the improved patients in an attempt to discover what type of patient is helped by cortisone. The improved patients were not significantly different from the mean of the entire experimental group in both pretreatment and post-treatment ACTH responsivity. With reference to 17-ketosteroid excretion, it can be seen from table V that no initial difference existed between the entire group and the 9 patients who eventually improved. While the group as a whole did show a rise in 17-ketosteroid levels at the end of therapy, those who did improve exhibited a significant mean decrease in 17-ketosteroid excretion. Examination of the individual changes did not reveal any unanimous decrease in 17-ketosteroid output in the improved patients. The 17-ketosteroid level in 2 patients increased and remained the same in 1 patient. The trend, however, seems to have been toward decreased levels.

Preliminary reports* on the experimental patients showed changes in the electroencephalograms after the cortisone treatment. Frequency analysis of the electroencephalograms suggests that the specific foci of cortisone are on the 9 and 16 cycle-per-second frequencies. In four instances of aberrated discharges in both the lower (3 cycle-per-second) and higher (22 cycle-per-second) frequencies, these were brought to a level comparable with the controls. It is possible that aside from its specific focal action (reticule activating center), cortisone may have some generalized homeostatic action on cortical controls.

* This work was performed by Creed Ward, M. D.

Toxic Effects: An internist* examined all patients in the study before, during, and after administration of the drug. Before treatment a complete examination was made including blood count, urinalysis, serology, EKG, and chest x-ray. During the course of treatment blood pressure, body weight, peripheral edema, and any untoward complications were noted. The physical examination was repeated when the therapy ended to check for any obvious comparative changes.

Although the dosage of cortisone was relatively large in most instances, the toxic manifestations were minor and few in number. Rounding of the face and peripheral edema were observed in only 4 of the 21 patients receiving cortisone. Only 6 patients showed a gain in weight and an elevation of systolic blood pressure in excess of 20 mm. of mercury. In no instance was the drug discontinued because of outward reactions. In the later stages of treatment costovertebral angle pain and hematuria occurred in 3 patients, 2 of whom had a history of prior episodes of similar pain. The clinical findings suggested renal colic, but in each case the hematuria subsided spontaneously before its etiology could be determined. The only other toxic manifestation was marked oliguria in 1 patient, which persisted for 18 to 24 hours with recovery following conservative treatment.

One final result may have some bearing on the prognosis of cortisone treatment. All patients were placed in one of two categories on the basis of their social history. Those who apparently had made a good prepsychotic adjustment were classified in one group as opposed to those who had adjusted poorly before the onset of their illness. Forty-one per cent of the experimental group fell into the former category and 59 per cent in the latter. Frequency of improvement was 56 per cent and 31 per cent respectively.

DISCUSSION

The number of patients, 42.8 per cent, showing improvement after cortisone therapy is most favorable when the type of patient included in the experiment is taken into consideration. The sample was made up of subjects whose prognoses were extremely poor. Where electrocoma, insulin, and in some cases lobotomy had failed, treatment with cortisone brought about sufficient improvement in 9 patients, who otherwise would have been committed for more or less permanent hospitalization. The characteristics of the sample, therefore, would add weight to the conclusion that cortisone can be helpful in the treatment of psychoses.

The type of psychotic disturbance in which cortisone is of value cannot be adequately answered at present, since the number of patients in each of the schizophrenic subgroups is too small. The overlapping of diagnostic categories further affects such an analysis. Some patients with hebephrenic features showed paranoid traits at other times during their illness, a not unusual finding. Actually, the paranoid patients made the most progress of any subgroup on cortisone therapy, but again their number is too small to reach any definitive con-

* Doctor William F. Dowdell performed the examinations in this part of the study.

clusion. However, this category is at least worthy of further study in relation to steroid hormone therapy.*

The chief conclusion to be drawn from the psychologic test results is that no sizeable number of patients made any striking improvement or revealed outstanding changes in personality structure or function. Most of the post-treatment records remained psychotic in nature even though some tendencies were psychologically favorable. Three possible reasons for the slight improvement seen in the entire experimental group are: (1) practice effects, (2) wearing off of ECT, which most patients had received as little as several days before the pretreatment psychologic testing, or (3) the actual effects of cortisone. In this study, increases in M + or in F + percentage scores and the decrease in the number of Rorschach cards failed cannot be attributed to practice, but these measures can be affected by ECT. Quite possibly, the slight improvement was due to the longer interval between ECT and the second psychologic testing.

The relationship between previous treatment with electrocoma and insulin and the results obtained with cortisone similarly cannot be evaluated. It has been noted in previous clinical reports[8, 9] that patients who had not responded to months of electrocoma therapy did respond remarkably after the administration of cortisone. It may be inferred from this that cortisone produces sufficient change in the adrenal gland of the chronic schizophrenic to make electroshock an effective therapeutic measure.

The same indefinite conclusions must necessarily be drawn about dose levels and duration of treatment. The objective was to achieve some partial adrenal atrophy, but how this can be best accomplished with cortisone depends upon the development of an adequate measure of adrenocortical function and its alterations. The four day trial by Rees[24] certainly would seem too small in time to produce any change.

Eosinophil counts, 17-ketosteroids, and ACTH responsivity were employed as the indices of adrenocortical function. The results summarized in table IV indicate the wide difference in the mean eosinophil response of the experimental group to a test dose of 25 mg. ACTH before and after cortisone treatment. On the basis of this test, the experimental patients, prior to treatment, had an adequate adrenal response. The subsequent administration of cortisone for a period of one month apparently decreased the patient's ACTH responsivity, probably by producing partial adrenal atrophy.

The eosinophil levels were carefully measured but showed the same broad variations reported by other investigators. No consistent trend could be discerned in any of the patients over a prolonged period. At least in this study, the extreme variability of the eosinophil level made it a very poor index of adrenocortical function from which no meaningful results could be determined.

Although the difference in the pretreatment and post-treatment 17-ketosteroid levels is significant, such change, in so rough an index of adrenocortical function, is not large enough

* No depressives were treated with the exception of one involutional patient. The clinical impression is that cortisone seems almost contraindicated in the involutional psychoses. The involutional patient did very poorly on cortisone. One reason for exacerbation of the illness may be that cortisone lowers the production of androgenic hormones, which are believed to have beneficial effects in male involutional psychoses.

TABLE IV

Pretreatment and Post-Treatment ACTH Responsivity and 17-Ketosteroid Evaluations for the Experimental Group

Measure	Mean Pre-Rx	Mean Post-Rx	Difference	t
ACTH Responsivity	−63.6%	−30.6%	−33.0%	5.1*
Ketosteroids	21.0	24.5	+3.5	2.34†

* Significant beyond .01 level of confidence.
† Significant beyond .05 level of confidence.

TABLE V

Pretreatment and Post-treatment 17-Ketosteroid Excretion of Entire Experimental Group and of "Improved" Experimental Patients

	Mean Pre-Rx	Mean Post-Rx	Difference
Experimental Group	21.0±1.92	24.5±2.94	3.5
Improved Patients	21.8	18.9	2.9
Difference	+0.8†	−5.6*	

* Significantly lower than mean of entire group beyond .01 level of confidence.
† Not statistically significant.

to justify any final decisions. The value of this index is open to question when its levels are affected, as Long[17] and Altschule and Parkhurst[5] have pointed out, by substances of diverse function from the adrenal gland in both sexes and the gonads in males. Just why 17-ketosteroid excretion in the improved patients decreased is unknown, unless it can be considered a beneficial effect of partial adrenal atrophy. Altschule[4] found that patients who improved after electroshock had lower 17-ketosteroid rates than before such therapy and also that animals subjected to ECT revealed moderate degrees of adrenal atrophy. To explain the higher than normal excretion of 17-ketosteroids in schizophrenia, Hoagland and Pincus[13] theorize that it is due to the increased output by the adrenal of its precursors. The relationship between 17-ketosteroid excretion and adrenal function is too complex for so direct a conclusion. It fails to take into account the unknown variable effect of other androgenic steroids on the daily 17-ketosteroid levels.

Recent progress in adrenal physiology has made these three indices of adrenocortical function less and less satisfactory. Thorn,[26] it is true, has stated that ACTH responsivity is a more specific measure of adrenocortical response than any other method generally available. The measurement of urinary cortins by Hoagland and Pincus,[13] while a more direct approach, is subject to the same variable hazards as the 17-ketosteroid index. The Sweat[24] and Porter-Silber[22] methods of measuring blood corticoid levels, which give definite levels of

fractions B and F by an accepted biochemical process, have aroused expectations of perfecting an index free of these objections.

Until an adequate index is developed, it cannot be determined beforehand what patients give evidence of adrenocortical function which might be improved by cortisone treatment. Seventeen-ketosteroids, eosinophil counts, ACTH responsivity, and other known tests do not satisfactorily distinguish between patients who can and those who cannot benefit from cortisone therapy. The newer blood corticoid indices may provide the basis for this delimitation and perhaps some understanding why cortisone succeeds in some cases and not in others.

The minimal toxic symptoms produced by the prolonged high doses of cortisone were quickly reversible at the termination of treatment. No residuals or sequelae have occurred in any of our patients. There were no changes in the chest x-rays of the 21 experimental patients. Any patient whose pretreatment reading indicated tuberculous activity was excluded from the experimental group, but this finding of no change in the experimental patients gives little support to the notion that cortisone is responsible for breaking down old tuberculous lesions of the chest.

In repeating the study by Castor et al[7] of the pathologic effects of cortisone on the brain of rats, the preliminary results reported by the pathologists* confirm that cortisone ingestion by rats causes paraventricular degeneration of the thalamic nuclei. Significantly, this is the area in which degeneration has been noted as an effect of the classical type of lobotomy. It raises the interesting possibility that behavioral changes after cortisone treatment may be related to the effect of cortisone on these nuclei.

The analysis of the electroencephalograms taken before and after the experiment failed to show any consistent relationship between cortisone treatment and changes in brain wave patterns. This result does not confirm previous studies reporting specific, detailed changes in brain waves of patients receiving cortisone. Woodbury and Sayers,[38] for example, demonstrated that cortisone lowers the electroshock seizure threshold and increases brain excitability. The results of this study are decidedly more in line with Lidz and his co-workers,[16] who found no correlation between electroencephalograms and changes in mood induced by cortisone.

CONCLUSION

Whether cortisone therapy in mental illness should be abandoned or continued cannot be answered without further investigation and experimentation. A great deal of additional data must first be gathered before any conclusion can be reached. Nine of the 21 psychotic patients treated with cortisone improved significantly. Until an adequate and direct measure of adrenocortical function is perfected, we shall not have clear-cut evidence for the possible benefit to be derived from treating psychotic patients with any of the adrenal steroids.

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* This study will be reported separately by Donald Hackel, M. D., and Richard D. Rubin, M. A.

SUMMARY

Twenty-one patients were treated with doses of cortisone varying from 300 to 500 mg. daily for a period of one month; 42.8 per cent showed significant improvement.

The three indices of adrenocortical function employed, 17-ketosteroids, eosinophil levels, and ACTH responsivity, did not differentiate adequately between the patients both before and after treatment.

No serious toxic effects resulted from the treatment.

Future investigation should be based on a direct method of measuring adrenocortical function, specifically blood corticoid levels, in order to evaluate adrenal function in psychotic illnesses. This will be a sound basis for the possible use of steroids as therapeutic agents in psychiatry.

RESUMEN

El 42,8 % de 21 pacientes tratados con dosis de cortisona que oscilaron entre 300 y 500 mg. diarios, por un período de un mes, mostraron una mejoría ostensible.

Los tres índices empleados de la función adrenocortical, 17-cetosteroides, prueba de la eosinopenia provocada y respuesta al ACTH, no se diferenciaron apreciablemente entre los pacientes, antes y después del tratamiento y como resultado del mismo, no se observaron serios efectos tóxicos.

Una futura investigación debe ser basada en un método directo para la medida de la función suprarrenocortical, específicamente sobre la concentración de corticoides en la sangre para evaluar la función suprarrenal en los enfermos psicóticos. Esto constituirá una base sólida para el posible uso de los esteroides como agentes terapéuticos en Psiquiatría.

RESUME

Vingt-et-un sujets ont été traités par la cortisone administrée en doses quotidiennes variant de 300 à 500 mg. pendant une période d'un mois; on a observé une amélioration sensible dans 42,8 pour cent des cas.

Les trois indices de fonction adréno-corticale employés, à savoir 17-cétostéroïdes, niveaux éosinophiles et sensibilité à l'ACTH, n'ont pas permis d'établir une différenciation suffisante entre les sujets tant avant qu'après le traitement. Le traitement n'a provoqué aucun effet toxique sérieux.

Les recherches devront à l'avenir être basées sur une méthode directe de mesure de la fonction adréno-corticale, plus spécialement des niveaux corticoïdes sanguins, dans le but d'évaluer la fonction adrénale dans les affections psychotiques. Ceci constituera une base rationnelle pour l'emploi éventuel des stéroïdes comme agents thérapeutiques en psychiatrie.

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Autonomic Nervous System Tests in Carbon Dioxide Inhalation Therapy

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Autonomic nervous system changes in mental illness have been observed by many investigators. The results of drugs which affect autonomic functions in mentally ill patients also have been studied. One of the more easily accessible autonomic functions is the blood pressure, which can be readily measured and recorded. In recent years considerable progress has been made in testing autonomic responses in a number of psychiatric disorders and in connection with various somatic therapies used in modern psychiatry.

In 1948, Funkenstein, Greenblatt, and Solomon[1] published a study of the effects of adrenergic and cholinergic stimulation as a test of the autonomic nervous system in mentally ill patients. These authors used epinephrine intravenously and mecholyl intramuscularly in patients of different diagnostic categories and reported seven different response patterns. None of these autonomic responses was found to be specific for any diagnostic group, but patients in two of their groups responded more favorably to electric shock therapy than those who fell into other groups. The authors concluded that individuals vary in their autonomic patterns but that these patterns can be altered by electric shock treatment or other methods of therapy.

In two subsequent publications, the same investigators[2, 3] further studied changes in the autonomic nervous system responses as determined by reactions to epinephrine and mecholyl. By subjecting the autonomic nervous system to stress with these adrenergic and cholinergic drugs, they made important observations of the organism's attempt to regain physiologic equilibrium or homeostasis. Evidence accumulated indicating that psychiatric changes of clinical proportions frequently are accompanied by changes in autonomic activity. While controls showed a moderate response to the two drugs with a definite tendency to re-establish homeostasis in a short time, psychiatric patients revealed either exaggerated or weak reactions to the drugs, often with deficient capacity to re-establish homeostasis. Based on these findings, Funkenstein, Greenblatt, and Solomon[4] attempted to predict the clinical effects of electroshock therapy in schizophrenic patients and suggested three characteristics for good prognosis with this treatment in schizophrenic patients: (1) initial grouping in two of their groups; (2) anxiety precipitated or relaxed by mecholyl; (3) a chill following mecholyl injection. In a more recent study, the same authors[5] reported that psychiatric patients with elevated blood pressure, when tested with mecholyl, fall into two groups—one in which the blood pressure drop remains below the preinjection level for over 25 minutes, and another

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in which the blood pressure returns to the original level sooner. According to the investigators, the first indicates excessive secretion of epinephrine, whereas the latter is assumed to be caused by excessive secretion of nor-epinephrine. The first group is said to respond favorably to electroshock therapy regardless of diagnostic category, and the latter shows little improvement with this treatment. They suggest utilizing this as a prognostic test prior to administration of electroshock.

What physiologic explanation of these findings in autonomic responses is possible? Gellhorn[6] in his recent book, *Physiological Foundations of Neurology and Psychiatry*, discusses these tests and concludes that mecholyl causes a sympathetico-adrenal discharge which depends on the state of excitability of the hypothalamus. He points out that if increased hypothalamic excitability exists, the blood pressure returns quickly to its normal level or may even show a compensatory rise, and that if there is a reduction in the response of the hypothalamus, the hypotensive action of mecholyl is prolonged. He believes that the mecholyl test is an indicator of the degree of hypothalamic sympathetic excitability. Gellhorn concludes that electroshock and other forms of shock treatment are indicated in patients with sympathetic hyporeactivity and that these treatments are contraindicated in patients with hyperreactive sympathetic centers.

Since carbon dioxide in high concentrations reduces hypothalamic reactivity, Gellhorn suggests that CO_2 inhalation therapy be used in psychiatric patients with sympathetic hyperreactivity of hypothalamic origin. To test this hypothesis the following study was made.

METHOD

Twenty-eight patients were studied with the mecholyl test before CO_2 treatment. Of these, 19 were tested before and after CO_2 therapy. All patients were male veterans, age 22 to 44, hospitalized on the Psychiatric Service of the Minneapolis Veterans Hospital. None of the patients was psychotic. Of the diagnostic categories, 11 were anxiety reactions, 8 somatization reactions, 4 depressive reactions, 2 conversion reactions, and 1 phobic, 1 mixed, and 1 immaturity reaction. The patients were given from 4 to 20 carbon dioxide inhalation treatments at the rate of three treatments per week. The average number of treatments per patient was 9.5, and the average number of respirations given was 20 per patient during each treatment.

Procedure of administering the mecholyl test was as follows. The test was made on the fasting patient lying in the supine position. The patient was reassured so as to be comfortable and as relaxed as possible in order to obtain a basal reading. The blood pressure was taken once a minute for a minimum of eight readings. In this period of eight or ten minutes the blood pressure became stabilized, or slowly rose and fell through a fairly fixed range. Ten mg. of mecholyl in 1 cc. of water was then injected fairly deep into the triceps muscle of the opposite arm. The systolic blood pressure was taken and recorded every half minute for six minutes after the injection, and then every minute for an additional twenty minutes. The measurements were recorded with the systolic blood pressure as the ordinate and the time as the abcissa.

RESULTS

Graph 1 shows that the blood pressure curves following injection of mecholyl can be classified into four different groups.

Table I indicates that of the 28 patients treated with CO_2 and psychotherapy, 8 showed marked improvement, 11 slight to moderate benefit, and 9 failed to improve. Of the 8 patients showing marked benefit, 4 were somatization reactions, 3 anxiety states, and 1 conversion reaction. It is of interest that all 4 patients with anxiety and conversion reactions had somatic symptoms pronounced enough to be included in their major diagnosis.

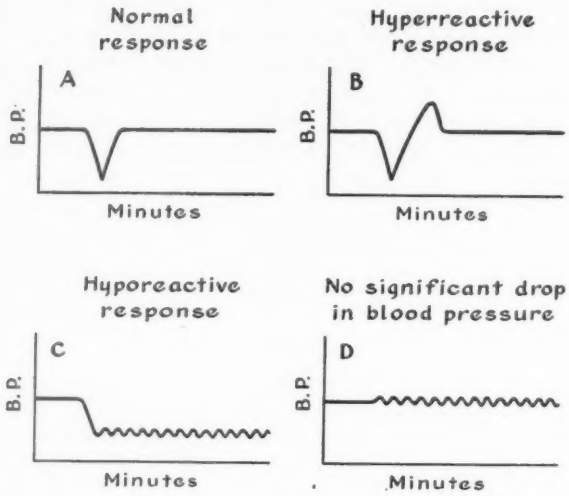

FIGURE 1. Four schematic blood pressure patterns after mecholyl injections.

As indicated in table I, of the 28 patients tested prior to CO_2 therapy, 10 showed a type D response (no significant drop in blood pressure). These reactions must necessarily be considered a test failure. Of these 10 patients, a post-CO_2 treatment test revealed the same type D response in 6 patients.

Of the 28 patients tested, the breakdown of the various responses before CO_2 therapy is as follows: 11 patients in Group A, 5 in B, 2 in C and 10 in D. Of the 19 patients tested before and after CO_2 treatment, 12 remained in the same group and 7 switched autonomic grouping in the following manner: 2 patients from A to D, 1 from A to B, and 1 each from B to D, C to A, D to A, and D to B. Patients who changed groupings showed the following response to the treatment: the 2 patients from A to D were markedly improved, from C to A and D to A also markedly improved, D to B and B to D moderately improved, and from A to B not improved.

TABLE I

Patients Tested with 10 mg. of Mecholyl Before and After Carbon Dioxide Therapy

No.	Pt.	Age	Mecholyl Group Before CO_2	Mecholyl Group After CO_2	Diagnosis	Clinical Response to CO_2 Therapy	Number of Treatments
1.	E.K.	29	D	D	Anxiety reaction	Slight	8
2.	H.L.	36	D	A	Somatization reaction	Marked	10
3.	O.S.	37	A	A	Immaturity reaction	None	11
4.	H.H.	25	B	D	Conversion reaction	Slight	11
5.	N.F.	33	A	A	Anxiety reaction with somatization	Marked	10
6.	D.J.	24	B	B	Anxiety reaction with somatization & schizoid trends	None	10
7.	G.E.	28	D	D	Reactive depression & immaturity	None	8
8.	D.L.	39	D	D	Somatization reaction with depression	None	17
9.	P.D.	30	D	D	Somatization reaction	Marked	11
10.	W.L.	42	C	C	Phobic reaction	Slight	20
11.	C.W.	44	A	D	Anxiety reaction with somatization	Marked	15
12.	S.S.	28	D	B	Anxiety reaction	Moderate	6
13.	I.T.	37	A	A	Anxiety reaction	None	9
14.	P.C.	26	A	D	Anxiety reaction with somatization	Marked	9
15.	C.S.	38	D	D	Anxiety reaction with depression	Slight	6
16.	P.C.	31	A	B	Anxiety reaction with somatization	None	9
17.	G.L.	29	D	D	Somatization reaction	Marked	6
18.	R.K.	32	B	B	Somatization reaction	Moderate	10
19.	L.R.	44	C	A	Somatization reaction	Marked	10
20.	H.S.	36	A		Anxiety reaction	Slight	8
21.	R.G.	28	A		Depressive reaction	Moderate	8
22.	G.E.	40	D		Depressive reaction	None	6
23.	A.H.	39	A		Anxiety reaction	None	7
24.	R.M.	22	D		Psychoneurosis, mixed, with schizoid trends	None	13
25.	L.K.	33	B		Conversion reaction with somatization	Marked	4
26.	J.V.	40	A		Depressive reaction	Slight	7
27.	M.M.	32	B		Somatization reaction	Slight	11
28.	H.D.	25	A		Somatization reaction	Slight	6

Of the 19 patients tested before and after CO_2 treatment, the group responses were as follows: prior to treatment 6 patients in Group A, 3 in B, 2 in C and 8 in D. Omitting the 8 patients with a type D reaction leaves 11 patients, of whom 6 remained in the same test group after CO_2 therapy, and five of these showed no remarkable improvement. Of the remaining five, 3 had a type D reaction in the post-treatment test. Of the remaining two patients in whom a change in grouping occurred, one moved from group A to B. He failed to benefit from CO_2 therapy. The other shifted from group C to A and definitely benefited from CO_2 treatment. Therefore, of 19 patients tested before and after CO_2 therapy, in

only one patient was the clinical change toward improvement correlated with the mecholyl tests. However, this patient's autonomic response did not indicate sympathetic hyperreactivity, but rather a hyporeactive pattern.

DISCUSSION

It is noteworthy that in over one third of the patients tested with mecholyl no significant drop in blood pressure occurred. This high number of test failures, to whatever cause it may be attributed, makes the reliability and general usefulness of this test as an indicator of autonomic function doubtful. The question as to whether or not a given patient will show the same response to mecholyl injection upon repeated tests also remains unanswered inasmuch as only one test was given each patient prior to carbon dioxide therapy. Distribution of diagnostic categories did not seem to correlate with autonomic grouping, substantiating the findings of Funkenstein, Greenblatt, and Solomon. However, of 11 patients showing a type A response (normal homeostasis), 6 were diagnosed as anxiety reactions. There was no moving from groups with a higher number to the lower numbers noted, as observed by previous investigators. Clinical improvement did not appear to be accompanied by a change in autonomic pattern, nor did it seem to be determined by belonging to a specific response group prior to treatment. Since none of the authors' patients had psychotic reactions, it appears advisable to apply the mecholyl test to this type of patient in an effort to duplicate the results of the Harvard group of investigators. It is possible that psychotic patients react in an entirely different manner to stress situations precipitated by drugs, as perhaps indicated by the relatively high number of normal homeostatic responses (type A) and test failures (type D) in our series of neurotic patients. In this connection attention is called to the findings of Gold,[7] who studied the reactions to mecholyl in 33 schizophrenic patients before and after insulin shock therapy. He reported that clinical improvement was accompanied by a decreased reaction to mecholyl and interpreted this as being due to an increase in the sympathetic nervous system reactivity in overcoming the parasympathetic stimulus.

Factors which play a role in maintaining blood pressure in response to internal and external stress are not confined to reactivity of the sympathetic centers in the hypothalamus. The kidneys, the posterior pituitary, and the adrenal cortex also play an important role in effecting homeostasis of this essential function. Especially in acute reactions to stress, the adrenal medulla may be of primary importance since the effects of the adrenal cortex are much slower. Funkenstein, Greenblatt and Solomon discussed their findings primarily in relation to electric shock therapy, which motivated them to propose a theory concerning the effective mechanism of this form of treatment. They believe that electroshock lowers basal sympathetic tension which has been increased by the illness. At the same time, the reactivity of the sympathetic nervous system to stimulation is increased. This, they claim, is accompanied by a decreased reaction of the parasympathetic nervous system to stimulation. They emphasize that these changes are merely physiologic concomitants of the basic psychologic changes and that there is no evidence that they are in any way of etiologic significance.

Gellhorn, on the other hand, relates mental illness to a dysfunction of the autonomic nervous system. He claims that in schizophrenia the sympathetic centers in the diencephalon are hyporeactive, and he ascribes the therapeutic effect of electroshock therapy to prolonged excitation on the hypothalamic sympathetic structures. In much the same way he applies a similar principle in considering the working mechanism of carbon dioxide therapy in psychoneurosis. He believes that the increased emotional reactivity of neurotic patients has its cause in a hyperreactive response of the posterior sympathetic hypothalamus and that carbon dioxide inhalation therapy restores hypothalamic reactivity to a normal level. He differs with Meduna,[8] who ascribes the effect of carbon dioxide in a physiologic theory of neurosis to a threshold-increasing action analogous to the effect of CO_2 on the peripheral nerve and proposes a theory for achieving homeostasis by turning positive feedback circuits into negative ones, for which experimental evidence is lacking.

However, high concentrations of carbon dioxide have been experimentally shown to diminish electrical potentials of the hypothalamus and hypothalamic-cortical discharges as well, as pointed out by Gellhorn,[9] who believes that CO_2 can diminish hypothalamic overexcitability and can cause long-lasting changes. It is of considerable prognostic significance, therefore, if tests which measure the state of reactivity of the hypothalamus can be applied prior to therapy to enable one to predict the outcome, effectiveness, and prognosis to a proposed form of treatment.

The authors' findings do not seem to support the theories described above. However, it would seem desirable to test them in a larger group of patients. Perhaps different dosage or technic may alter the ultimate findings. Furthermore, it seems essential to discover additional tests measuring hypothalamic function of sympathetic and parasympathetic responses, either with other drugs or by means of entirely new methods.

SUMMARY

1. Twenty-eight patients with psychoneurosis were studied with the mecholyl test before carbon dioxide therapy. Of these, 19 patients were tested before and after CO_2 treatment.

2. In over one third of the patients tested with mecholyl, no significant drop in blood pressure occurred.

3. Distribution of autonomic grouping did not correlate with diagnostic categories.

4. Clinical improvement was not accompanied by change in autonomic response, nor determined by a specific pre-treatment pattern.

5. The work of Funkenstein, Greenblatt, and Solomon and the theories of Gellhorn have been discussed.

RESUMEN

Funkenstein, Greenblatt y Solomon, han estudiado los efectos de las drogas adrenérgicas y colinérgicas sobre la presión arterial en pacientes mentales, y comunicaron que en dos de sus grupos han respondido favorablemente a la terapia con el electrochoque, que fueron acompañados de cambios en la actividad autonómica. Estas pruebas de la actividad auto-

nómica se han usado con el propósito de predecir los efectos clínicos de la terapia por elel electrochoque en pacientes esquizofrénicos. Gellhorn entiende que la prueba del mecolil es indicadora del grado de excitabilidad simpática hipotalámica y sugiere que la terapia por el electrochoque o por la insulina, está indicada en pacientes con hiporreactividad simpática y que el tratamiento por inhalación de anhidrido carbónico (porque reduce la reactividad hipotalámica), sea usado en pacientes con hiperactividad simpática de origen hipotalámico.

Para probar estas hipótesis, fueron estudiados 28 pacientes psiconeuróticos con la prueba de mecolil (10 mg. de mecolil intramuscularmente, en 1 c. c. de agua) antes de ser tratados con CO_2. De este número de pacientes, 19 fueron sometidos a la prueba antes y después de la terapia con CO_2 y todos eran veteranos del Ejército, cuya edad oscilaba entre los 22 y 44 años.

El promedio de tratamientos por paciente, fue de 9,5 y de 20 el de inhalaciones durante cada tratamiento. Se describen 4 tipos de presión arterial: normal, hiperreactivo, hiporreactivo y sin descenso ostensible en la presión arterial (fracaso de la prueba).

En uno solo de los 19 pacientes probados con CO_2, se observó una mejoría clínica en relación con los resultados de la prueba con mecolil. Sin embargo, la respuesta autonómica de este paciente no indicó hiperreactividad simpática, sino más bien una tendencia hiporreactiva. En más de un tercio de los pacientes probados con mecolil no se registraron descensos ostensibles de la presión arterial.

Este alto numero de fracasos de la prueba, cualquiera que sea su causa, hace discutible su seguridad y utilidad general como indicadora de la functón autonómica. La distribución de los grupos, según las características de su sistema autonómico, no guarda relación con las categorías diagnósticas. La mejoría clínica no fue acompañada por cambios en la respuesta autonómica, ni determinada por un tipo específico en el período anterior al tratamiento.

RESUME

Funkenstein, Greenblatt et Solomon ont étudié les effets des médicaments adrénergiques et cholinergiques sur la tension artérielle chez des sujets aliénés et ont rapporté que les malades de deux de leurs groupes ont réagi favorablement à la thérapeutique par choc électrique avec changements concomitants dans l'activité autonome. On a eu recours à ces essais autonomes dans le but de s'efforcer de prédire les effets cliniques de la thérapeutique par choc électrique chez les sujets schizophrènes. Gelhorn est d'avis que l'essai au mécholyle est un indice du degré d'excitabilité sympathique hypothalamique. Il suggère que la thérapeutique par choc électrique ou à l'insuline est indiquée pour les sujets à hyporéactivité sympathique, et qu'il y a lieu de mettre en oeuvre la thérapeutique à inhalation d'anhydride carbonique (parce qu'elle diminue la réactivité hypothalamique) dans les cas de malades souffrant d'hyper-réactivité sympathique d'origine hypothalamique.

Afin de vérifier cette hypothèse, 28 sujets ont été étudiés par l'essai au mécholyle (administration par voie intramusculaire de 10 mg de mécholyle dans 1 cm^3 d'eau) avant le traitement au CO^2; sur ce groupe, 19 ont été soumis aux essais avant et après la thérapeutique au CO^2. Ces sujets étaient d'anciens combattants, âgés de 22 à 44 ans. Le nombre moyen de traitements par sujet a été de 9,5 et le nombre moyen d'inhalations reçues a été de 20

pendant chaque traitement. Quatre types de tension artérielle sont décrits: type normal, type hyper-réactif, type hypo-réactif, et type sans chute appréciable de tension artérielle (absence de réaction à l'essai).

Sur 19 sujets soumis aux essais avant et après la thérapeutique au CO^2, un seul malade a accusé une corrélacion entre la tendance clinique à l'amélioration et les essais au mécholyle. Toutefois, la réaction autonome de ce malade n'a pas révélé d'hyper-réactivité sympathique, mais au contraire une tendance du type hypo-réactif. Chez plus d'un tiers des sujets essayés au mécholyle, on n'a observé aucune chute appréciable de la tension artérielle. Ce nombre élevés d'échecs à l'égard de cet essai, quelle que soit la cause à laquelle on les attribue, montre que cette méthode est peu sûre et d'une utilité générale plutôt douteuse comme indice de la fonction autonome. La répartition du groupement autonome n'a pas établi de corrélation avec les catégories diagnostiques. L'amélioration clinique n'a pas été accompagnée d'un changement de la réaction autonome, pas plus qu'elle n'a été déterminée par un type de prétraitement particulier.

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Complications Resulting From Protracted Insulin Coma

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In 1934, Sakel introduced insulin shock treatment to psychiatry. Our knowledge of the effect of this treatment is as yet inadequate, but owing to its advantageous effect on numerous mental disorders it cannot be dispensed with.

In the course of time, a series of complications of varying degree arising out of this treatment have become known, the most serious of them being the protracted coma, from which the patient does not always recover, even after having been given sufficient amount of glucose. The final outcome of such a protracted coma may be complete recovery, partial recovery with various physical or mental defects, or even death. In certain investigations, the rate of mortality has been estimated as high as 16 per cent. The most common causes of death are heart failure and pneumonia.

The physiologic mechanism of this protracted coma is not exactly known. Spencer, who has collected 83 cases of protracted coma from literature and analyzed them, finds that the majority of cases of protracted coma occur during the first fortnight of treatment. The depth of coma and the duration of the effect of the insulin given are both important; even a lower degree of hypoglycemia may result in protracted coma if lasting for a sufficiently long period. A state of postcoma confusion in a patient is an indication that he may be subject to protracted coma in the course of the succeeding days. Spencer is of the opinion that changes occurring to other organs than the brain also come into the picture, e.g., complications which may affect the carbohydrate metabolism. In this connection, he especially points to the effect of hypoglycemia on the cortex of the suprarenal gland as shown by Waaler and Jansen. Sindell holds that a condition of angiospasms in the brain is a factor of major importance for bringing about an insulin coma, considering the results obtained by the use of vasodilatory substances on coma patients. Braunmühl stresses changes in the carbohydrate metabolism in the tissues, vascular damage, and changes in water and salt content of the blood. Investigators have also demonstrated that the carbohydrate metabolism and the consumption of oxygen in the brain decrease during coma. Easton holds that the asthenic type of bodily constitution is more easily subject to protracted coma than other types.

The pathologic anatomic changes resulting from the protracted coma are especially revealed as degenerations of the cerebral cells of the temporal and frontal lobes, degenerations of the basal ganglia, diffuse glia-cell proliferation, and hypertrophy of the endothelium. Spencer suggests as a prophylactic measure a slow increase of the doses of insulin given

during treatment together with short and not too deep comas. During the treatment, it is important that the patient be given adequate food with a high vitamin B content.

Braunmühl holds that the quantity of insulin to be given in each dose must be considered when changes in the patient's reaction to insulin appear and by difficulties connected with bringing the patient back to consciousness.

In the Neevengaarden Mental Hospital, 276 patients were given insulin shock treatment from 1947 to June, 1952. In the 5 cases presented here, serious complications in connection with coma occurred.

CASE HISTORIES

Case number 1: The patient, a 37 year old woman of the pyknic type, had been diagnosed as a schizophrenic with periodic catatonia. From the age of 25, the patient had been noticeably difficult and nervous, and at one period she was in a mental hospital for four weeks. In August, 1947, she was again admitted to the Neevengaarden Mental Hospital in a periodically confused condition. A series of electroshock treatments were administered, and insulin therapy was also given. On January 21, 1948, after the tenth injection of insulin (140 I. U.), fifth coma, the patient could not be brought back to consciousness despite four injections of heavy doses of glucose. The patient, who remained in a coma for 16 days, was treated with plasma, fluid, food, stimulants, oxygen, and penicillin. Gastric juice containing blood was aspirated. On the fourth day of protracted coma, fits and twists of the head were observed. Although the case was further complicated by bronchopneumonia, the patient gradually recovered. During the first weeks after regaining consciousness, the patient was depressed, stubborn, and in a state of mutism. However, she gradually improved and five months later was discharged and went to live with her family. She had become calm, content, even-tempered, but gave an impression of being childish (I.Q.—8 years). When seen 27 months after the protracted coma, the subject appeared gentle and kind, but distracted and uncritical (I.Q.—13.4 years). At this time, she was no longer classed as a mental patient by the hospital.

Case number 2: The patient was a 45 year old man of the pyknic type whose diagnosis was melancholic depression. His condition was characterized by feelings of anxiety and a proneness to suicide. Before admission to Neevengaarden Mental Hospital, he had received electroshock treatments, which were discontinued due to a fracture of the spine.

Insulin shock treatment was given to the patient, and the first coma occurred on the tenth day of treatment. After 21 days of treatment, he had his eighth coma (with 240 I.U.); and he was brought back to consciousness in the usual way. The following day, the subject was put in a coma and remained in coma of varying depths for five days. A spinal puncture was made and the pressure found to be 300 mm. Treatment instituted consisted of intravenous glucose, stimulants, vitamin B, and removal of spinal fluid. Inhaling of amyl nitrite appeared to be of some effect on the depth of the coma. The blood sugar level remained normal. Two days after the patient had regained consciousness, he had epileptoid fits consisting of tonic and clonic movements of the left leg, and he seemed dazed. His skin was warm and sweaty. This state lasted for two days.

Following the coma, the patient was in an euphoric, stupefied condition with a period of amnesia and confabulation. Upon neurologic examination, a number of findings were made: masklike expression on the face, dysarthria, slight left-side paresis of seventh cerebral nerve, restricted movability of upper left limb with atrophy of muscles and rigidity pointing to a lesion of the basal ganglions. There were also a slowing of movements and reduced strength of the limbs, the body generally spastic. Reflexes of the upper left limbs and lower limbs were good: plantar reflexes were doubtful. In the course of the following days, neurologic examinations indicated some improvement, and the patient's mental condition seemed to be better. An attempt was made to keep the patient in a private home, but he had to return to the hospital because of the severe mental deterioration. The patient has remained in the same mental state, inattentive to cleanliness, careless in his dressing, uses bad language, has a poor memory, and is inconsiderate and irritable. Previous to his illness, he was a conventional person of good mental ability.

Case number 3: This subject was a man of the pyknic type, 50 years of age, with the diagnosis of manic-depressive. The patient had a rash on his scalp that spread over his face during spells of depression. From the age of 17 years, the patient had been drinking heavily. In August, 1945, at the age of 45, he was admitted to Neevengaarden Mental Hospital in a state of confusion and agitation with hallucinations and ideas of persecution. He was discharged in December, 1946, but had to be readmitted one and a half years later. During his stay at the hospital, periods of depression and hypomania alternated. Electroshock treatment was effective but only temporarily so. The patient was discharged again a year later after receiving insulin shock treatment —37 comas. No complications resulted from the insulin treatment.

The patient was admitted once more to the same hospital in December, 1950, in a depressed condition. There were short periods of improvement after electroshock therapy. Insulin shock treatments were administered, and the first coma occurred on the eleventh day of therapy. The second coma occurred on the thirteenth day of treatment (May 11, 1951) with 220 I. U. During that afternoon, the patient appeared confused and was given sugar orally. Insulin shock treatment was discontinued. On the following day, the patient was depressed and refused his food; and the next day, he became highly confused, negativistic, and restless. Because of urine retention, he was given 1 cc. doryl I.M. but without effect. Half an hour later, in order to alleviate the patient's restlessness, he was given ½ mg. hyoscine. It was noticed that after this treatment the subject remained quiet for several hours. Therefore, a combined doryl-hyoscine treatment was tried the next day with the same results. In the following weeks, a left-side lesion of the pyramidal tract gradually became noticeable, inverted plantar reflex on the left foot, general increase of deep reflexes on the left side, weakening of the abdominal reflexes on the 'eft side, and slight muscular atrophy of the left leg. Subsequent development of the patient's condition has been characterized by a greater frequency of depressed periods and increasing irritability.

Case number 4: This patient was a pyknic woman, 62 years of age, with a diagnosis of schizophrenia. Her disorder was one of long-standing, and she was admitted to the Neevengaarden Mental Hospital from private care in 1930. Her condition was that of dementia with frequent catatonic attacks. She suffered from contractures in both legs and never left her bed unless she was in a highly angered state. Since her disorder continued, uninfluenced by a frontal leucotomy, insulin shock treatment was started on November 11, 1952. Dose was increased to 120 I. U. but was soon lowered to 100 I. U. because it became difficult to awaken the patient and adrenalin was required a few times. On December 17, after 21 injections—eighth coma, following 100 I. U. administered at 6:50 a.m., her coma at 10:25 a.m. was so deep that it had to be broken with adrenalin and I.V. glucose. After regaining full consciousnesses, she ate and drank a large amount; at about 1:00 p.m. she complained of a headache and pains in her right leg. Then she had an epileptic fit starting in the right side. During the attack, a deviation of the eyeballs upwards and to the left was observed. This was followed by a series of convulsions during which the patient remained fully conscious and responded to simple questions with a yes or no answer. Despite the glucose, which was given several times I.V. (total amount—304 cc. of a 25 per cent solution) and the usual sedatives, the patient had six fits during the day, succeeded by seven that night. The next day she had a single fit, and after an interval of three days she experienced a series of three fits on the same day. Blood sugar level was normal: her temperature was slightly high the first three days (38.3 C.) then gradually dropped to normal.

The patient recovered in a short period of time, and some months later she could sit up and talk with visitors. However, she suffered a relapse, and now she has periods when she either scolds everyone or speaks very little. However, she seems more content and is much easier to contact.

Case number 5: The patient was a 49 year old asthenic woman with a diagnosis of constitutional psychosis. She had Graves disease and for the last few years had been under treatment in the medical ward of the hospital. Since 1949, she has had illusions and hallucinations of a depressive type, combined with strong feelings of inferiority. Because she was in poor physical condition, her only treatment was a careful insulin medication to stimulate her appetite. The doses did not exceed 25 I.U. After three months of treatment, one morning, by accident, the patient was given 70 I.U. instead of the prescribed 10 I.U. She was all right in the morning, but during the afternoon, she lapsed into a coma. She recovered and nothing unusual was noticed until the following

morning when she relapsed into another coma from which she recovered after glucose, oxygen inhalation, and adrenalin were given. She had a remarkable mental change after the protracted coma in that her depression developed into a manic state of several days' duration. However, several weeks later she had improved enough to leave the hospital.

SUMMARY

Of 276 cases treated with insulin shock therapy at Neevengaarden Mental Hospital serious complications occurred in only 5 cases. In these five patients, of whom 4 were pyknics, there was no correspondence between the duration and depth of the coma and the degree of the resulting defect.

The first coma occurred in three patients on the sixth, tenth, and the eleventh day of treatment respectively; doses were 140 I.U., 240 I.U., and 220 I.U. In all 3 cases, the level of blood sugar remained normal during the protracted coma. In 1 case, the coma became temporarily less pronounced after inhalation of amyl nitrite. One patient, who had been in a state of confusion, recovered completely for several hours after he was given doryl followed with hyoscine half an hour later. One patient had a very high pressure of the spinal fluid during the protracted coma. This finding is not in accordance with Spencer's observations.

The first patient remained in coma for 16 days followed by considerable mental improvement. There were no signs of brain lesions afterward. The second patient was in a coma for 5 days. He remained in a state of physical and mental deterioration. Clinical symptoms indicate lesions in the brain cortex and the basal ganglia.

The third patient was comatose for 10 minutes, followed by a period of confusion. Afterwards, there was a greater frequency of depressive periods and increased irritability plus permanent slight left-side lesions of the pyramidal tract.

The fourth case of protracted coma was unusual because the patient suffered from convulsions when conscious and was able to answer simple questions. As in earlier reported cases, her blood sugar level remained normal during days of coma. How far her abnormal reaction to insulin may be considered a result of changes that had taken place in her brain as a result of frontal leucotomy remains an unanswered question. Since epileptic fits after this operation are not uncommon, it is possible that an acquired irritability may play a part.

The fifth case, which also deserves special attention, concerns a patient who after given a relatively moderate dose of insulin turned from deep depression into a sudden manic state, although of only a few days' duration. The authors assume that the sudden overflow of insulin in an organism as exhausted as hers, and suffering from a previous hyperthyroidism, may have brought some serious disturbance of the balance of hormones.

RESUMEN

Sólo en 5 de 276 casos que requirieron ser tratados por el choque insulínico en el Neevengaarden Mental Hospital, se registraron complicaciones serias. En estos cinco pacientes, de los cuales 4 eran de hábito pícnico, no hubo correlación entre la duración y profundidad del coma y el grado de lesión resultante.

El primer coma ocurrió en 3 pacientes en el sexto, décimo y undécimo día de tratamiento, respectivamente. Las dosis fueron de 140 U. I., 240 U. I. y 220 U. I. En los tres casos el nivel de la glucemia continuó normal durante el período de coma prolongado. En un caso el coma se hizo temporalmente menos pronunciado después de la inhalación de nitrito de amilo. Un paciente que se había encontrado en estado de confusión, mejoró completamente durante varias horas, después de habérsele administrado doril, seguido de hioscina media hora más tarde. Otro paciente tuvo hipertensión del líquido cefalorraquídeo durante el coma prolongado. Este hallazgo no está de acuerdo con las observaciones de Spencer. Se presentan en este trabajo debidamente detalladas, las historias clínicas de 5 casos.

RESUME

Sur 276 cas qui ont nécessité le traitement de choc par l'insuline à l'Aisle d'Aliénés de Neevengaarden, on n'a observé de complications sérieuses que dans 5 cas. Pour ces 5 cas, dont 4 étaient des cas pykniques, on n'a relevé aucune correspondence entre la durée et la profondeur du coma et le degré du défaut résultant.

Le coma initial s'est produit chez 3 sujets respectivement le sixième, le dixième et le onzième jour du traitement; les doses administrées ont été de 140 U.I., 240 U.I. et 220 U.I. Dans la totalité des 3 cas, la teneur sanguine en sucre s'est maintenue normale pendant toute la période de coma prolongé. Dans un de ces cas, le coma est devenu temporairement moins prononcé après l'inhalation de nitrite d'amyle. Un autre de ces sujets, qui avait été dans un état de confusion, a accusé un état parfaitement normal pendant plusieurs heures après avoir reçu une dose de doryle suivie, une demi-heure plus tard, de l'administration d'hyoscine. Un autre sujet a accusé une très forte pression du liquide spinal pendant le coma prolongé: cette constatation ne s'accorde pas avec les observations de Spencer. Cinq cas d'observations sont présentés en détail.

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NOTICE

By the request of Doctor Finn Rud the following changes should be made on his paper, "Euthanasia," which appeared in the January, 1953, issue of this journal. Page 8, line 5, stupid should be stuporous; page 8, line 5 of the poem should read—"With the blow-pipes cunning wile;" page 8, line 11 of the poem should read "My soul" instead of "Her soul;" and on page 9, line 34, it should read "(2) I do not believe, i.e., as atheist."

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